Enantioselective organocatalytic Michael additions to acrylic acid derivatives: generation of all-carbon quaternary stereocentres†

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Received (in Cambridge, UK) 27th March 2008, Accepted 14th May 2008
First published as an Advance Article on the web 25th June 2008
DOI: 10.1039/b805233f

Acrylic esters, thioesters and *N*-acryloyl pyrrole have been identified as effective electrophiles in the enantioselective Michael addition reaction with β-keto ester pro-nucleophiles catalysed by a cinchona alkaloid derived bifunctional organocatalyst; enantiomeric excesses of up to 98% and yields of up to 96% can be obtained for a range of Michael acceptors and pro-nucleophiles.

The asymmetric Michael addition of acidic methine pro-nucleophiles to electron deficient alkenes is a direct and powerful method for the production of all-carbon quaternary stereogenic centers bearing pendant functionality amenable to further derivatisation. Since Wynberg's description[1] of the cinchona alkaloid catalysed addition of cyclic β-keto esters to methyl vinyl ketone, several examples of catalytic asymmetric Michael additions of carbon acids to the simplest, β-unsubstituted Michael acceptors leading to adducts in high enantiomeric excess have been reported. α,β-Unsaturated ketones,[2,3] acrolein,[2,3] acrylonitrile[4] vinyl sulfones[4] and ethylidene bisphosphonate esters[5] are all effective electrophiles using both metal-[2] and metal-free catalysis.[3–5] Asymmetric Michael additions to acrylate derivatives leading to adducts with tertiary stereogenic centres in moderate to high enantiomeric excesses are known through chiral phase transfer catalysis,[6] however, the direct formation of acrylate Michael adducts bearing fully substituted quaternary stereogenic centres in high enantiomeric excess under catalytic metal-free conditions has, to our knowledge, yet to be reported, despite the synthetic potential of such a methodology.[6e,7] Through employment of cinchona alkaloid-derived bifunctional organocatalysts developed in our, and other, laboratories (Fig. 1),[8–10] we believed the discovery of a highly enantioselective variant was plausible and accordingly began investigations.

Initial studies were required to assess the reactivity profile of various acrylate esters. Indanone-derived β-keto ester **2** was chosen as the test pro-nucleophile on the basis of its high reactivity in other Michael addition reactions. Ethyl acrylate **3a**, ethyl thioacrylate **3b** and 1-naphthylthioacrylate **3c** were then screened in the reaction using 3 equivalent of Michael acceptor and DABCO (1,4-diazabicyclo[2.2.2]octane) at 10 mol% as catalyst. The results are presented in Table 1.

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† Electronic supplementary information (ESI) available: Experimental procedures and spectral data for compounds **3c**, **3d**, **3f**, **3g**, **11**, **4c–4i**, **12c–18c**, **20** and **21**. CCDC 683070. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b805233f

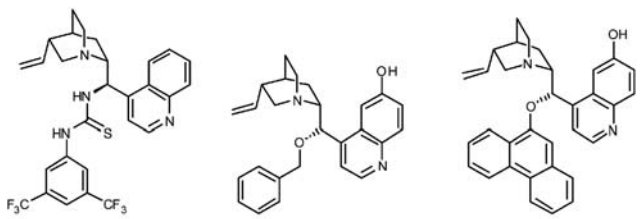
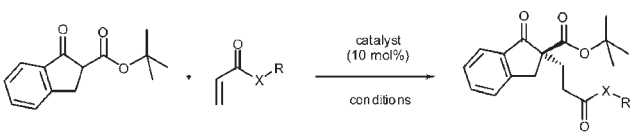


Fig. 1 Bifunctional cinchona alkaloid-derived organocatalysts.

With either ethyl acrylate **3a** and ethyl thioacrylate **3b** none of the desired Michael adducts were observed after stirring in CH_2Cl_2 at room temperature for 7 days. However, with 1-naphthylthioacrylate **3c** rapid and clean conversion to the desired Michael adduct **4c** was observed (entry 3, >95% conversion after 30 min). With suitable reactivity established, attention turned towards the development of the catalytic asymmetric variant. An encouraging 40% ee was observed using 10 mol% catalyst **1b**,[8a–c] however this could be increased significantly to 82% by the use of catalyst **1c**[4a,8f–i] instead. Optimisation of this result by examination of various reaction parameters resulted in a further increase of ee to 90%; finally, a change of catalyst to the slightly bulkier phenanthrene substituted catalyst **1d**[4a,8f–i] further increased the ee to 96%.

Table 1 Reactivity and optimisation studies[a]



2 **3a**: X = O, R = Et; **3b**: X = S, R = Et; **3c**: X = S, R = 1-naphthyl → **4a**: X = O, R = Et; **4b**: X = S, R = Et; **4c**: X = S, R = 1-naphthyl

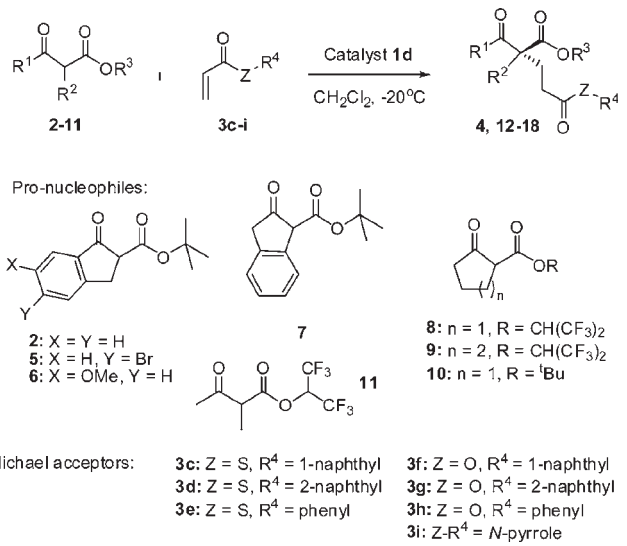
Entry	E^+	Cat.	Solv.	c^b/M	T/°C	Conv.^{c} (%)	ee^d (%)
1	**3a**	**1a**	CH_2Cl_2	1	r.t.	0	—
2	**3b**	**1a**	CH_2Cl_2	1	r.t.	0	—
3	**3c**	**1a**	CH_2Cl_2	1	r.t.	>95	—
4	**3c**	**1b**	CH_2Cl_2	1	r.t.	>95	40
5	**3c**	**1c**	CH_2Cl_2	1	r.t.	>95	82
6	**3c**	**1c**	CH_2Cl_2	1	0	>95	86
7	**3c**	**1c**	CH_2Cl_2	1	−20	>95	88
8	**3c**	**1c**	CH_2Cl_2	0.33	−20	>95	90
9	**3c**	**1c**	PhMe	0.33	−20	>95	82
10	**3c**	**1c**	THF	0.33	−20	>95	74
11	**3c**	**1d**	CH_2Cl_2	0.33	−20	>95	96

[a] Reaction was carried out using 3 equivalents of Michael acceptor and 10 mol% catalyst: see ESI† for experimental details and full optimisation table. [b] Concentration of **2**. [c] Determined by ^{1}H NMR analysis. [d] Determined by HPLC.

The tolerance of these optimised reaction conditions towards a variety of pro-nucleophiles was then investigated (Table 2). Substituted indanone esters **5** and **6** gave comparable results to those obtained using indanone ester **2** (entries 2 and 3); regioisomeric 2-indanone derivative **7** gave a slightly lower ee of 88% (entry 4). Cyclopentanone and cyclohexanone derivatives **8** and **9** were also found to be good substrates giving rise to the Michael adducts with high enantiocontrol, albeit with a prolonged reaction time in the latter case (entries 5 and 6). Notably, the hexafluoroisopropyl esters were found to be far superior to the *tert*-butyl ester analogues;[3a] cyclopentanone derivative **10**, bearing a *tert*-butyl ester moeity, gave only 67% ee after 18 h (entry 7) and its cyclohexyl analogue was found to be completely unreactive under the reaction conditions. Acyclic β-keto ester **11** was also found to react with **3c**, albeit more slowly and with a reduced enantioselectivity; product **18c** was obtained in 58% yield and 71% ee (entry 8).[11]

Next, the scope of the reaction with respect to the Michael acceptor was investigated. Comparable results were observed using thioacrylates **3d** and **3e** (entries 9 and 10); the reaction could also be extended to encompass the use of acrylate esters

Table 2 Scope of the Michael addition reaction[a]



Entry	Pro-nucleophile	Michael acceptor	*t*/h	Yield (%)	ee[b] (%)	Product
1	**2**	**3c**	2	83	96	**4c**
2	**5**	**3c**	0.5	78	93	**12c**
3	**6**	**3c**	0.5	90	94	**13c**
4	**7**	**3c**	1	95	88	**14c**
5	**8**	**3c**	1	75	95	**15c**
6	**9**	**3c**	96	52	98	**16c**
7	**10**	**3c**	18	64	67	**17c**
8	**11**	**3c**	120	58	71	**18c**
9	**2**	**3d**	2	75	95	**4d**
10	**2**	**3e**	2	83	95	**4e**
11	**2**	**3f**	72	83	94	**4f**
12	**2**	**3g**	72	76	94	**4g**
13	**2**	**3h**	72	78	94	**4h**
14	**2**	**3i**	3	96	95	**4i**

[a] Reaction was carried out in CH_2Cl_2 at −20 °C using 3 equivalents of Michael acceptor and 10 mol% catalyst: see ESI† for full experimental details. [b] Determined by HPLC.

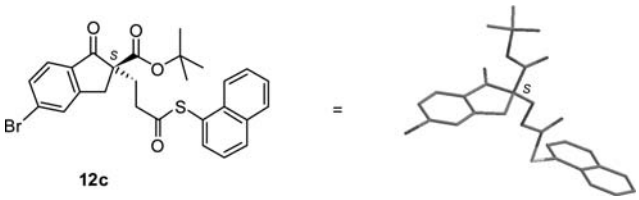
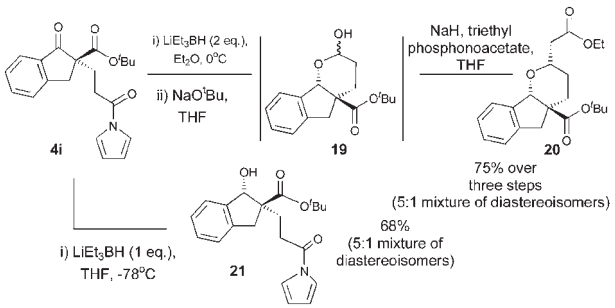


Fig. 2 Determination of absolute stereochemistry.



Scheme 1 Manipulation of *N*-acryloyl pyrrole Michael adduct **4i**.

such as **3f**, **3g** and **3h** (entries 11, 12 and 13). Recrystallisation of adduct **12c** to enantiopurity followed by single-crystal X-ray diffraction analysis allowed the *S* absolute stereochemical configuration of the major enantiomer to be assigned (Fig. 2). The absolute stereochemical configuration of all the other products was assigned by analogy.

The success of *N*-acryloyl pyrrole **3i** (entry 14) in this reaction is significant as *N*-acylpyrroles are valuable synthetic intermediates due to the unusual stability of the tetrahedral intermediate formed upon addition of a nucleophile.[12] To demonstrate this utility, adduct **4i** was treated sequentially with Super-hydride® followed by sodium *tert*-butoxide to generate lactol **19**; Wadsworth–Horner–Emmons olefination then afforded tetrahydropyran **20** (Scheme 1). The product was isolated as a 5 : 1 mixture of diastereoisomers; the stereochemistry of **20** as depicted in Scheme 1 was supported by NOE experiments on **20** itself and partially reduced indanol ester **21** (formed by treatment of **4i** with one equivalent of Super-hydride®).

To conclude, we have developed a highly enantioselective organocatalytic Michael addition of methine carbon acids to acrylic esters, thioesters and *N*-acryloyl pyrrole using a cinchona alkaloid-derived bifunctional organocatalyst. This reaction results in the formation of a quaternary stereogenic centre and generates adducts in high yields and up to excellent enantioselectivities. Further investigations in this field are ongoing and the results will be reported in due course.

We gratefully acknowledge the EPSRC (EP/D04961X/1) for funding (to C. L. R.) and Dr M. Helliwell for single-crystal X-ray diffraction analysis.

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